UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/869,677	10/09/2001	Lars Bjorck	100084.416USPC	8541

7590 03/01/2004

Patrick J O'Connell
Popovich & Wiles
Ids Center Suite 1902
80 South 8th Street
Minneapolis, MN 55402-2111

EXAMINER	
GRASER, JENNIFER E	

ART UNIT	PAPER NUMBER
1645	21

DATE MAILED: 03/01/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/869,677	BJORCK ET AL.	
	Examiner	Art Unit	
	Jennifer E. Graser	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *15 September 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11* is/are pending in the application.

4a) Of the above claim(s) *4-9* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,10 and 11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

Acknowledgment and entry of the Amendment submitted 12/28/03 is made. Claims 1-3, 10 and 11 are currently under examination. Claims 4-9 have been withdrawn because they are drawn to a non-elected invention. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Sequence Compliance

1. The instant specification contains several nucleotide/amino acid sequences in the text of the disclosure which are encompassed by the definitions for nucleotide/amino acid sequences as set forth in 37 C.F.R. 1.821(a)(1) and (a)(2) and which must conform with the sequence rules for all applications that include nucleotide/amino acid sequences. The sequence identifiers obtained through conformance (paper submission and CRF/electronic) must be inserted into the body of the specification directly following the sequence. See pages 19, line 27-page 20, line 3; page 26, line 24; page 27, lines 9-12; page 31, line 26. Additionally, Applicants are responsible for meeting compliance with any sequence the Examiner may have inadvertently missed. APPLICANT MUST COMPLY WITH THE SEQUENCE RULES WITHIN THE SAME TIME PERIOD AS IS GIVEN FOR RESPONSE TO THIS ACTION, 37 C.F.R. 1.821-25. Failure to comply with these requirements will result in ABANDONMENT of the application under 37

C.F.R. 1.821(g). Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 C.F.R. 1.136. In no case may an applicant extend the period for response beyond the six month statutory period.

NOTE: These sequences were inadvertently missed by the Examiner at the time of the first Office Action. Accordingly, this action will not be made Final.

Drawings

2. The drawings are objected to as failing to comply with 37 CFR 1.84(p)(4) because in Figure 1 reference character "mtsA" has been used to designate both 'mtsB' and 'mtsC'. Figure 1 shows the mtsA, mtsB and mtsC genes of the IraI operon. See the 'Brief Description of Drawings' for Figure 1 in the paragraph bridging pages 3-4. Correction is required.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 1-3, 10 and 11 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1 and 2 are vague and indefinite because part (c) of said claims reads on fragments of variants. This language encompasses polypeptides which have not been disclosed

in the specification, i.e, a fragment of a variant could include the amino acids which vary from the protein of SEQ ID NO:2. See 112, 1st enablement rejection below.

Claims 1 and 2 are vague and indefinite because it is unclear what is encompassed by the term "variant". Is this a completely different protein? Does it include substitutions, deletions and insertions? The use of the term 'immunogenic fragment' is preferable.

Parts (b) and (c) of claims 1 and 2 attempt to define the invention by results to be achieved which merely amounts to the statement of the underlying problem, i.e., providing a polypeptide which binds specifically to a MtsA polypeptide having the amino acid of SEQ ID NO:2 or generates an immune response to Streptococcus". The structural and technical features for achieving this result should be present in the claim which would allow for one to identify the protein without ambiguity. Additionally, claims 1 and 2 are also vague and indefinite because part (c) of the claims refers to fragments of 'at least 60 amino acids in length', but does not require these amino acids to be from SEQ ID NO:2 or for them to be contiguous. Rather, these could be 60 amino acids with a sequence completely different than SEQ ID NO:2 and contain amino acids which are from the 5% that is not from SEQ ID NO:2. Accordingly, the metes and bounds of the claim cannot be understood.

Claim Rejections - 35 USC § 112-Scope of Enablement

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to

make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claim 1 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for 'an isolated and purified polypeptide comprising the amino acid sequence of SEQ ID NO:2 and immunogenic fragments thereof which are at least 60 amino acids in length'; and for 'an isolated and purified polypeptide which is 95% identical to a protein having the amino acid of SEQ ID NO:2 and which specifically bind an antibody which binds specifically to a MtsA polypeptide having the amino acid sequence of SEQ ID NO:2', does not reasonably provide enablement for 'variants having at least 95% identity to a protein having the amino acid sequence of SEQ ID NO:2 and which specifically bind an antibody which binds specifically to a MtsA polypeptide having the amino acid sequence of SEQ ID NO:2'; or for fragments *from the variant* which are at least 60 amino acids in length (this language does not require the 60 amino acids to be from SEQ ID NO:2 let alone a contiguous stretch). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The breadth of the instant claims contains proteins and peptides other than what is specified in the sequence disclosure. The specification states that substitutions, additions, or deletions may be made to the defined sequences, i.e., "variants"; however, the specification provides no guidance as to what amino acids may be changed without causing a detrimental effect to the protein to be produced. Further, it is unpredictable as to which amino acids could be removed and which could be added. While it is known that many amino acid substitutions

are possible in any given protein, the position within the protein's sequence where amino acid substitutions can be made with a reasonable expectation of success are limited. Other positions are critical to the protein's structure/function relationship, e.g., such as various positions or regions directly involved in binding, catalysis in providing the correct three-dimensional spacial orientation of binding and catalytic sites. These regions can tolerate only very little or no substitutions. Selective point mutation to one key antigen residue eliminate the ability of an antibody to recognize this altered antigen. If the range of decreased binding ability after single point mutation of a protein antigen varies, one could expect point mutations in the protein antigen to cause varying degrees of loss of protection, depending on the relative importance to the binding interaction of the altered residue. Alternatively, the combined effects of multiple changes in an antigenic determinant could again result in loss of protection. A protein having multiple antigenic sites, multiple point mutations, or accumulated point mutations at key residues could create a new antigen that is precipitously or progressively unrecognizable by any of the antibodies in the polyclonal pool. Thus, proteins of different levels of homology may not induce antibody which is recognized by the "native" protein of the *Streptococcus* bacteria, and be ineffective in a vaccine composition against *Streptococcus*. Additionally, because part (c) of the claims refers to fragments of 'at least 60 amino acids in length', but does not require these amino acids to be from SEQ ID NO:2 or for them to be contiguous. Rather, these could be 60 amino acids with a sequence completely different than SEQ ID NO:2 and contain amino acids which are in the 5% that is not identical to SEQ ID NO:2. No disclosure, beyond the mere

mention of variants is made in the specification. While Applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of fragments, usually defined by an amino acid sequence, falling within the scope of the claimed genus. A mere wish or plan for obtaining the claimed polypeptide is not sufficient. With the exception of SEQ ID NO:2, and immunogenic fragments thereof which are at least 60 contiguous amino acids in length'; and for 'an isolated and purified polypeptide which is 95% identical to a protein having the amino acid of SEQ ID NO:2 and which specifically binds to an antibody which binds specifically to a MtsA polypeptide having the amino acid sequence of SEQ ID NO:2', the skilled artisan cannot envision the detailed structure of the encompassed polypeptide variants and fragments of the variants (which include amino acid sequences not set forth in disclosure) and, therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate enablement and written description requires more than a mere statement that it is part of the invention and a reference to a potential method of isolating it. The molecule itself is required.

Claim Rejections - 35 USC § 112-Enablement

7. Claims 2, 3, 10 and 11 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claim 2 suffers from the same enablement issues regarding the structure of the polypeptide as set forth in the scope of enablement rejection above. Additionally, claims 2, 3, 10 and 11 are drawn to vaccines and methods of vaccinating against *Streptococcus* infection. Applicants have not shown that the full-length protein as set forth in SEQ ID NO:2 is effective as a vaccine. The specification does not provide any examples which demonstrate that the protein can generate an immunoprotective response. While the specification has shown that the protein is immunogenic and can induce antibodies in mice, it does not demonstrate that these antibodies can protect against *Streptococcus*. In order to enable a "vaccine" or a "method of vaccinating" against a disease caused by a bacterium such as *Streptococcus*, challenge experiments have to be shown. The bacterial vaccine art is highly unpredictable and often times a protein is capable of generating antibodies, yet is then shown to be ineffective in protecting against disease. However, methods of "treating" do not require as stringent a test.

The specification also has not identified any specific fragments or variants which could protect against disease caused by a *Streptococcus* strain (claim 3). The location of "protective" epitopes has not been provided. Often it takes more than one epitope to provide protection. Accordingly, claims to synthetic protective epitope(s) , fragments and variants are not enabled. Additionally, there is no correlation that a fragment, peptide or variant which binds a protein having the amino acid sequence of SEQ ID NO:2 would be protective.

Applicants have provide no guidance to enable one of ordinary skill in the art how to determine, without undue experimentation, the effects of different amino acid substitutions and

the nature and extent of the changes that can be made, nor have they identified specification location of epitopes which are protective. Given the lack of guidance contained in the specification and the unpredictability for determining acceptable amino acid substitutions, one of skill in the art could not make or use the broadly claimed invention without undue experimentation.

Response to Applicants' Arguments:

Applicants have stated that the skilled person would readily be able to test peptides which fall within the scope of claim 2 for their ability to generate an immunprotective response in an animal. This has been fully and carefully considered but is not deemed persuasive. As stated above, the bacterial vaccine art is highly unpredictable. Many bacterial proteins are shown to generate a good immune response *in vitro* and *in vivo*, yet are totally ineffective as vaccines for protecting against infection with wild-type bacteria. Additionally, the instant claims are drawn to polypeptides which are variants and fragments of variants which differ greatly from SEQ ID NO:2. The specification has not even enabled the full-length protein as a vaccine. In order to enable the protein for use as a vaccine, challenge experiments would need to be shown. The standard for a 'vaccine' is much higher than an 'immunogenic composition'. The former requiring challenge results which show there is protection from the wild-type bacterium, the latter only requiring an antibody response. Additional evidences must be provided in order to obtain the scope which covers this protection, i.e, results from challenge experiments. It is noted that 'immunogenic compositions' or 'pharmaceutical compositions' and 'methods of treating' do

not require as much evidence. Lastly, challenge experiments with the full-length protein will not be sufficient to enable smaller fragments or variants for use as a vaccine. The specification has not identified any specific fragments or variants which could protect against disease caused by a *Streptococcus*. The location of "protective" epitopes has not been provided. Often it takes more than one epitope to provide protection.

8. Correspondence regarding this application should be directed to Group Art Unit 1645. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Remsen. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15,1989). The Group 1645 Fax number is (703) 872-9306 which is able to receive transmissions 24 hours/day, 7 days/week.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer E. Graser whose telephone number is (571) 272-0858. The examiner can normally be reached on Monday-Friday from 7:00 AM-4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith, can be reached on (571) 272-0864.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (571) 272-1600.

JEGraser 2/25/04

Jennifer Graser
Primary Examiner
Art Unit 1645